(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number
WO 2004/007482 A2

(51) International Patent Classification[7]: C07D 403/00

(21) International Application Number:
PCT/US2003/022479

(22) International Filing Date: 16 July 2003 (16.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/396,424	16 July 2002 (16.07.2002)	US
60/402,490	9 August 2002 (09.08.2002)	US

(71) Applicant *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, Petah Tiqva 49131 (IL).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NISNEVICH, Gennady** [IL/IL]; 81/70 Netive Hen Str., 32688 Haifa (IL). **RUKHMAN, Igor** [IL/IL]; 1/11 Junior Stuff Dorms, Technion City, Haifa 32000 (IL). **PERTSIKOV, Boris** [IL/IL]; 3/4 Nativ Harimon, 36781 Nesher (IL). **KAFTANOV, Julia** [IL/IL]; 84/4 Haaliya Hashniya Str., 35471 Haifa (IL). **DOLITZKY, Ben-Zion** [IL/IL]; Lohame HaGhetto 32, 49651 Petach Tiqva (IL). **SHAPIRO, Eugeny** [IL/IL]; 18/1 Gut Levin St., Haifa 32922 (IL). **YAHALOMI, Bonit** [IL/IL]; Zinger 6, Kiryat Bialik 27037 (IL).

(74) Agents: **BRAINARD, Charles, R.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004-1050 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/007482 A2

(54) Title: NOVEL SYNTHESIS OF IRBESARTAN

(57) Abstract: Provided is a novel synthesis of irbesartan employing a phase transfer catalyst. Also provided is irbesartan having a fine particle size.

NOVEL SYNTHESIS OF IRBESARTAN

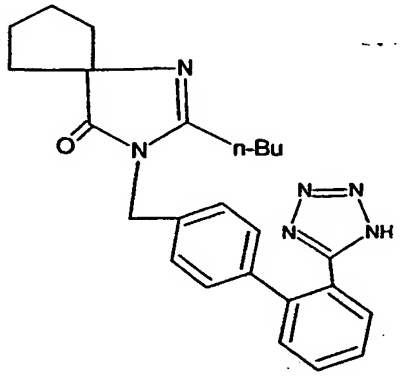
The present invention relates to a novel synthesis of irbesartan.

RELATED APPLICATIONS

The present Application claims the benefit of the filing date of United States Provisional Patent Applications 60/396,424, filed July 16, 2002, and 60/402,490, filed August 9, 2002.

BACKGROUND OF THE INVENTION

Irbesartan is a known angiotensin II receptor antagonist (blocker). Angiotensin is an important participant in the renin-angiotensin-aldosterone system (RAAS) and has a strong influence on blood pressure. The structure of irbesartan is shown below (I).



(I)

The synthesis of irbesartan is discussed, *inter alia*, in United States Patents 5,270,317 and 5,559,233; both of which are incorporated herein in their entirety by reference. In the synthesis therein disclosed, the prepenultimate reaction step (exclusive of work-up and purification) involves the reaction of a cyano group on the biphenyl ring with an azide, for example tributyltin azide. Reaction time as long as 210 hours can be required. *See,e.g.*, '317 patent.

United States Patent 5,629,331 also discloses a synthesis of irbesartan from a precursor 2-*n*-butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one with sodium azide using a dipolar aprotic solvent. As acknowledged in the '331 patent, there are safety risks involved in the use of azides (column 4, line 39). Also,

dipolar aprotic solvents (*e.g.* methyl pyrrolidone) are relatively high boiling and can be difficult to remove.

There is a need for an improved synthetic route to irbesartan.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a method of making irbesartan including the step of reacting 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system having first and second phases.

In another aspect, the present invention relates to a method of making irbesartan including the step of reacting 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system having first and second phases, wherein the first phase includes a first solvent that is an aromatic or aliphatic hydrocarbon and the second phase includes water and an inorganic base, for example KOH, NaOH, or LiOH, especially KOH.

In another aspect, the present invention relates to a method of making irbesartan including the step of reacting 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst that is a quaternary ammonium compound in a reaction system having first and second phases, wherein the first phase includes a first solvent that is an aromatic or aliphatic hydrocarbon and the second phase includes water and an inorganic base, for example KOH, NaOH, or LiOH, especially KOH.

In yet another aspect, the present invention relates to a method of making irbesartan including the steps of reacting 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of tetrabutylammonium hydrogensuflate in a reaction system having first and second phases, wherein the first phase includes a first solvent that is toluene and the second phase includes water and an inorganic base, especially KOH.

In still yet a further aspect, the present invention relates to 2-butyl-3-[2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one

made by a process comprising the step of reacting 2-butyl-1,3-diaza-spiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system comprising first and second phases.

In yet another embodiment the present invention relates to 2-butyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one made by a process comprising the step of reacting 2-butyl-1,3-diaza-spiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system comprising first and second phases.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is schematic diagram of the process for making irbesartan of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel synthesis of irbesartan in a two-phase reaction system having first and second liquid phases. The reaction is carried out in the presence of a phase transfer catalyst.

The first and second phases include first and second solvents, respectively, which are substantially immiscible in each other so that, when combined in a reaction vessel, a two-phase system is formed. Solvents are substantially immiscible in each other when equal volumes of them are mixed together, a two-phase system is formed in which the volume of the two phases is essentially equal. Preferably, substantially immiscible solvents are soluble in each other to the extent of about 1% (weight basis) or less.

First solvents can be aromatic or aliphatic hydrocarbons. Preferred first solvents are aromatic hydrocarbons. Examples of preferred aromatic hydrocarbons include benzene, toluene, m-xylene, o-xylene, and the tetralins, to mention just a few. Other aromatic hydrocarbons useful in the practice of the present invention will be apparent to the skilled artisan. Toluene is a particularly preferred aromatic hydrocarbon for use as first solvent.

The second solvent includes water. Water can be used alone or, preferably, an inorganic base such as KOH, NaOH or LiOH, to mention just a few, is combined with the water. The preferred inorganic base is KOH. Preferably, the water of the second phase

contains a molar amount of base that is about 7 to about 12 times the molar amount of the diazaspiro or biphenyl reactants discussed below.

Phase transfer catalysts are well known to one skilled in the art of organic synthesis. Phase transfer catalysts are of particular utility when at least first and second compounds to be reacted with each other have such different solubility characteristics that there is no practical common solvent for them and, accordingly, combining a solvent for one of them with a solvent for the other of them results in a two-phase system.

Typically, when such compounds are to be reacted, the first reactant is dissolved in a first solvent and the second reactant is dissolved in a second solvent. Because the solvent for the first reactant is essentially insoluble in the solvent for the second reactant, a two-phase system is formed and reaction occurs at the interface between the two phases. The rate of such an interfacial reaction can be greatly increased by use of a phase transfer catalyst (PTC).

Several classes of compounds are known to be capable of acting as phase transfer catalysts, for example quaternary ammonium compounds and phosphonium compounds, to mention just two. Tetrabutylammonium hydrogensulfate is a preferred PTC for use in the practice of present invention.

In a first step of the synthetic method of the present invention, 2-butyl-3-[2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one (IRB-03) is obtained. In this step, a first solution of 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole (IBR-02) in a first solvent is provided. IBR-02 is known in the art and is disclosed, for example, in United States Patent 5,128,355, the disclosure of which is incorporated herein in its entirety by reference.

Also to be provided is a second solution that includes 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one (IBR-01), water, PTC, and a base, preferably an inorganic base, most preferably, KOH. The base is present in an amount between about 7 and about 12 molar equivalents relative to the number of moles of IBR-01. 2-Butyl-1,3-diazaspiro[4.4]non-1-ene-4-one is known in the art and is disclosed, for example, in United States Patent 5,559,233, which has been incorporated herein by reference.

The first and second solutions, and their constituents, are combined in any order to form a two-phase reaction system that has first and second phases. The combining can be

in any suitable vessel that is equipped with means for vigorous agitation of the reaction system to maximize the interfacial area between the two phases. The combining can be at any temperature from about 20° C to about 95° C, preferably at about 90°C. The reaction is allowed to proceed in the two phase system for a time that the skilled artisan will known to adjust according to the reaction temperature. When the reaction temperature is about 90° C, a reaction time between about 1 and about 2 hours is usually sufficient.

After the reaction time and to facilitate phase separation, the reaction system is allowed to cool, preferably to a temperature of about 15°C to about 30°C and the first (organic, aromatic hydrocarbon) and second (aqueous) phases are separated. If desired, the aqueous phase can be extracted one or more times with toluene and the extract(s) combined with the first (organic, aromatic hydrocarbon) phase. Solvent is removed from the separated first phase, preferably by evaporation, especially at reduced pressure, to afford a crude residue.

In a second step of the synthetic method of the present invention, the trityl group is cleaved from the tetrazole ring. Crude residue is dissolved in a suitable water-miscible solvent. A solvent is water miscible if it is miscible with water at least in any proportion from 80:20 to 20:80 (weight basis). Acetone is a preferred water-miscible solvent. The resulting solution is acidified, preferably with a mineral or sulfuric acid, and agitated at a temperature between about 15°C and about 30°C. The time of the cleavage reaction can be conveniently monitored using thin layer chromatography. The acid is neutralized (that is, the solution is basified) with a molar excess of base, preferably and inorganic base, most preferably aqueous KOH. The basification is to a pH of about 8 to about 12, preferably to a pH of about 9 to about 10.5. Water-miscible solvent is evaporated, preferably at reduced pressure, to concentrate the basified solution whereby a suspension id formed. The order of basification and evaporation is not important. That is, water-miscible solvent can be first evaporated, followed by basification of the concentrate.

The trityl alcohol formed is separated and the liquid phase is acidified (e.g. to a pH of about 2 to about 3.5), preferably with mineral acid, most preferably with HCl. The resulting suspension is cooled and the product recovered by, for example, filtration. If desired, the isolated product can be washed with an organic solvent, preferably a lower aliphatic alcohol, most preferably *iso*-propanol, and dried, preferably at reduced pressure.

In another embodiment, the present invention provides fine particle size or "micronized" irbesartan in

cluding a plurality of irbesartan particles wherein the mean particle size ($d_{.05}$) is about 2 μm to about 7 μm and 10 volume percent or less of the plurality of particles have a particle diameter equal to or greater than about 30 μm, preferably 20 μm.

Micronized irbesartan including a plurality of irbesartan particles can be obtained by comminution using a fluid energy mill, wherein the mean particle size ($d_{.05}$) produced is about 2 μm to about 7 μm and 10 volume percent or less of the plurality of particles have a particle diameter equal to or greater than about 10 μm.

A fluid energy mill, or "micronizer", is an especially preferred type of mill for its ability to produce particles of small size in a narrow size distribution, i.e., micronized material. As those skilled in the art are aware, micronizers use the kinetic energy of collision between particles suspended in a rapidly moving fluid (typically air) stream to cleave the particles. An air jet mill is a preferred fluid energy mill. The suspended particles are injected under pressure into a recirculating particle stream. Smaller particles are carried aloft inside the mill and swept into a vent connected to a particle size classifier such as a cyclone. The feedstock should first be milled to about 150 to 850 μm which may be done using a conventional ball, roller, or hammer mill.

The starting material may have an average particle size of about 20-100 microns.

The material is fed into the micronization system in a controlled feed rate by means of a screw feeder or a vibratory feeder. The air jet mill is operated with controlled air pressures. For the Microgrinding MC-500 KX, the feed rate is 40-80 kg/hr, the Feed air pressure is 6-8.5 bar and the grinding air is 3-6 bar.

Micronizationization can also be accomplished with a pin mill. The starting material may have an average particle size of about 20-100 microns. The material is fed into the mill system in a controlled feed rate by means of a screw feeder or a vibratory feeder. The mill is operated with controlled speed. For the Alpine UPZ 160, the feed rate is 60-75 kg/hr, the mill speed is 7,000-15,000 rpm.

Micronized irbesartan can be used to make pharmaceutical compositions that can be in the form of solid oral dosage forms, for example compressed tablets. Compressed

tablets can be made by dry or wet granulation methods as is known in the art. In addition to the pharmaceutically active agent or drug, compressed tablets contain a number of pharmacologically inert ingredients, referred to as excipients. Some excipients allow or facilitate the processing of the drug into tablet dosage forms. Other excipients contribute to proper delivery of the drug by, for example, facilitating disintegration.

The present invention can be illustrated in one of its embodiments by the following non-limiting example.

Examples

Example 1:

A solution of KOH (10.4 g, 157.0 mmol), IRB-01 (12.0 g, 52.0 mmol) and Bu_4NHSO_4 (1.8g, 5.3 mmol) in water (40 mL) was added to a solution of IRB-02 (24.6 g, 44.1 mmol) in toluene (240 mL), and the resulting two-phase mixture was heated at 90°C with vigorous stirring for 1.5 hours. The mixture was cooled to room temperature, the phases were separated, and the aqueous phase was extracted with toluene (50mL). The combined organics were evaporated; the residue was dissolved in acetone (100 mL) and 3N HCl (52 mL, 156 mmol, 3 eq) and stirred at room temperature (TLC monitoring). A solution of KOH (14.6 g, 260 mmol, 5 eq) in water (100 mL) was slowly added, and acetone was evaporated under reduced pressure. The precipitate formed (trityl alcohol) was filtered and washed with water (2 x 50 mL); the filtrate was washed with toluene and slowly acidified to pH 4 with 3N HCl. The resulting suspension was cooled to 0-4°C, stirred for additional 30 min and filtered. The cake was washed with cold *iso*-propanol (2 x 25 mL) and dried under reduced pressure at 50-60°C; affording crude IRB-00 (14.5g, 33.8 mmol). Yield 84.3%, purity 94% (by HPLC).

Example 2:

A solution of H_2SO_4 (98 %, 22.6 g, 12.3 mL, 0.225 mol, 1.5 eq) in water (160 mL) was added to a suspension of IRB-03 (100.6 g, 0.150 mol) in acetone (600 mL) at 35-40 °C and stirred for 7 h (suspension disappeared; TLC monitoring – Hexane / EtOAc = 1:1). Acetone was evaporated from the reaction mixture under reduced pressure at 30-40 °C.

Water (500 mL) was added to the resulting suspension. The resulting mixture was vigorously stirred and cooled to 0-5 °C. A solution of KOH (85 %, 39.6 g, 0.600 mol, 4 eq) in water (100 mL) was slowly added keeping the reaction temperature below 15 °C

and the mixture was stirred for 30 min until a stable pH (9-10) was obtained. Then, a second portion of KOH (3.0 g, 50 mmol, 0.3 eq) in water (10 mL) was added and the reaction was stirred for additional 30 min at 5-10 °C (pH 10.5-11.5). The precipitate (triphenyl methanol) was filtered, washed with water (2 x 100 mL) and dried under reduced pressure (10 mmHg) at 50 °C to give 36.5 g (about 95 % yield) of triphenyl methanol. The aqueous filtrate was extracted with ethyl acetate (300 mL), cooled to 10 °C and acidified to pH 2.0–3.5 with slow addition of 20 % aqueous H_2SO_4. The resulting suspension was stirred at 0-4 °C for an additional 30 min and filtered. The filter cake was washed twice with water (2 x 100 mL), then with EtOAc (100 mL) and dried under reduced pressure for 3 h at 50 °C afforded 60.0 g (93 % yield) of crude Irbesartan. The crude product (60.0 g) was refluxed in 95 % aqueous ethanol (600 mL) for 1 h (clear solution was formed) and allowed to cool to room temperature with vigorous stirring. The mixture was stirred for an additional 2 h at 0-5 °C, filtered, and washed with cold 95 % aqueous ethanol (100 mL). The collected solid was dried under reduced pressure (3 h, 50 °C, 10 mmHg) afforded 56.0 g (93 % yield), of a white powder.

What is claimed is:

1. A method of making 2-butyl-3-[2'-(triphenylmethyl tetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one comprising the step of reacting 2-butyl-1,3-diaza-spiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system comprising first and second phases.

2. The method of claim 1 wherein the first phase comprises an aromatic or aliphatic hydrocarbon and the second phase comprises water.

3. The method of claim 2 wherein, prior to reaction, the 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one is in solution in aqueous base.

4. The method of claim 3 wherein the aqueous base is selected from the group consisting of KOH, NaOH and LiOH.

5. The method of claim 4 wherein the aqueous base is aqueous KOH.

6. The method of claim 2 wherein, prior to reaction, the 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole is in solution in an aromatic or aliphatic hydrocarbon.

7. The method of claim 6 wherein the 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole is in solution in an aromatic hydrocarbon that is toluene.

8. The method of claim 2 wherein the 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole is in solution in an aliphatic hydrocarbon.

9. The method of claim 1 wherein the phase transfer catalyst is a quaternary ammonium compound.

10. The method of claim 9 wherein the quaternary ammonium compound is tetrabutyl ammonium hydrogensulfate.

11. A method for making irbesartan comprising the steps of: preparing 2-butyl-3-[2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one prepared according to the method of claim 1; heating the combination to a temperature of about 20° C and about 95° C; separating the first and second phases; removing solvent from the first phase to obtain a residue; providing a mineral acid acidified solution of the residue in a water-miscible solvent, basifying the solution in water-miscible solvent with an inorganic base; removing water-miscible solvent from the solution; separating trityl alcohol so formed; and recovering irbesartan.

12. The method of claim 11 wherein the water miscible solvent is acetone.

13. The method of claim 11 wherein the basification is with an inorganic base to a pH of about 8 to about 12.

14. The method of claim 13 wherein basification with inorganic base is to a pH of about 9 to about 10.5.

15. 2-Butyl-3-[2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one made by a process comprising the step of reacting 2-butyl-1,3-diaza-spiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system comprising first and second phases.

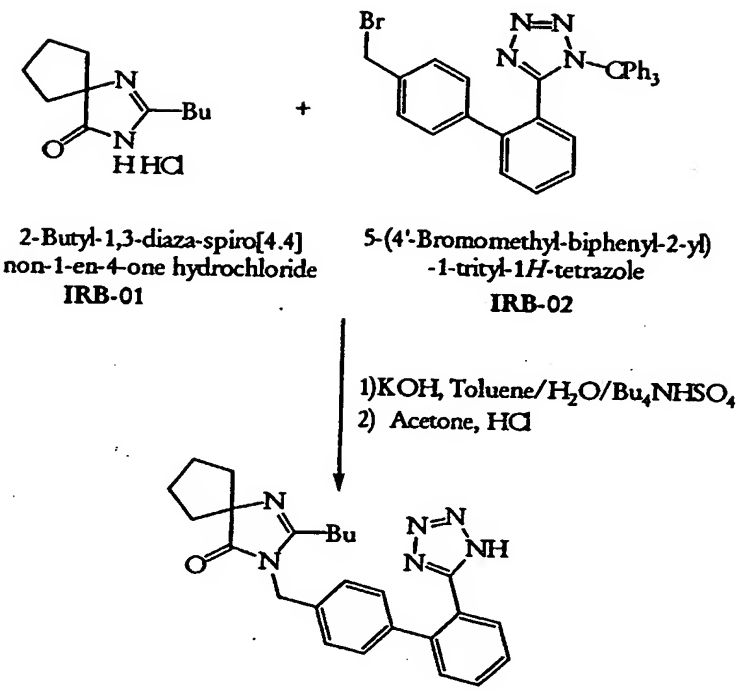
16. The 2-butyl-3-[2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one of claim 15 wherein the first phase comprises an aromatic or aliphatic hydrocarbon and the second phase comprises water.

17. 2-Butyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one made by a process comprising the step of reacting 2-butyl-1,3-diaza-spiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system comprising first and second phases.

18. The 2-butyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one of claim 17 wherein the first phase comprises an aromatic or aliphatic hydrocarbon and the second phase comprises water.

Figure 1

PTC Route to Irbesartan



2-Butyl-1,3-diaza-spiro[4.4] non-1-en-4-one hydrochloride
IRB-01

5-(4'-Bromomethyl-biphenyl-2-yl) -1-trityl-1*H*-tetrazole
IRB-02

2-Butyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.4]non-1-en-4-one

IRB-00

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number
WO 2004/007482 A3

(51) International Patent Classification[7]: C07D 403/10

(21) International Application Number:
PCT/US2003/022479

(22) International Filing Date: 16 July 2003 (16.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/396,424 16 July 2002 (16.07.2002) US
60/402,490 9 August 2002 (09.08.2002) US

(71) Applicant *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petaah Tiqva (IL).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NISNEVICH, Gennady** [IL/IL]; 23 Margalit Street, 34464 Haifa (IL). **RUKHMAN, Igor** [IL/IL]; 1/11 Junior Stuff Dorms, Technion City, 32000 Haifa (IL). **PERTSIKOV, Boris** [IL/IL]; 3/4 Nativ Harimon, 36781 Nesher (IL). **KAFTANOV, Julia** [IL/IL]; 84/4 Haaliya Hashniya Str., 35471 Haifa (IL). **DOLITZKY, Ben-Zion** [IL/IL]; Lohame HaGhetto 32, 49651 Petach Tiqva (IL).

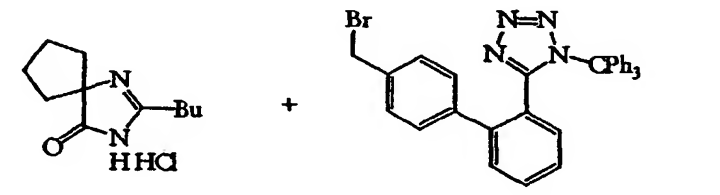
(74) Agents: **BRAINARD, Charles, R.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004-1050 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

[Continued on next page]

(54) Title: NOVEL SYNTHESIS OF IRBESARTAN

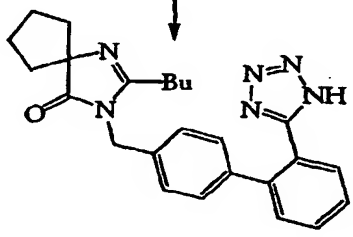
(57) Abstract: Provided is a novel synthesis of irbesartan employing a phase transfer catalyst. Also provided is irbesartan having a fine particle size.



2-Butyl-1,3-diaza-spiro[4.4] non-1-en-4-one hydrochloride
IRB-01

5-(4'-Bromomethyl-biphenyl-2-yl) -1-trityl-1*H*-tetrazole
IRB-02

1)KOH, Toluene/H_2O/Bu_4NHSO_4
2) Acetone, HCl



2-Butyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.4]non-1-en-4-one

IRB-00

WO 2004/007482 A3

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) **Date of publication of the international search report:**
27 May 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/22479

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 270 317 A (NISATO DINO ET AL) 14 December 1993 (1993-12-14) cited in the application	1-14
X	examples 5B,C	15-18
Y	WO 99 38847 A (SQUIBB BRISTOL MYERS CO) 5 August 1999 (1999-08-05) claims, examples	1-18
Y	LE BOURDONNEC, B.: "Synthesis and Pharmacological Evaluation of New Pyrazolidine-3,5-diones as AT1 Angiotensin II Receptor Antagonists" J. MED. CHEM., vol. 43, no. 14, 2000, pages 2685-2697, XP002259509 Scheme 2, step 19 -> 20-22	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2003	13/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stroeter, T

Form PCT/ISA/210 (second sheet) (January 2004)

BNSDOCID: <WO_____2004007482A3_I_>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/22479

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5270317 A	14-12-1993	FR	2659967 A1	27-09-1991
		FR	2665702 A1	14-02-1992
		FR	2681067 A1	12-03-1993
		AT	167475 T	15-07-1998
		AU	641005 B2	09-09-1993
		AU	7561091 A	21-10-1991
		CA	2057913 A1	21-09-1991
		CS	9100745 A2	12-11-1991
		CZ	287225 B6	11-10-2000
		DE	69129606 D1	23-07-1998
		DE	69129606 T2	17-12-1998
		DK	454511 T3	06-04-1999
		EP	0454511 A1	30-10-1991
		ES	2119764 T3	16-10-1998
		FI	103407 B1	30-06-1999
		WO	9114679 A1	03-10-1991
		HK	1008918 A1	21-05-1999
		HU	67648 A2	28-04-1995
		HU	61284 A2	28-12-1992
		HU	9500555 A3	30-10-1995
		IE	910913 A1	25-09-1991
		IL	97612 A	31-08-1995
		IL	110820 A	27-11-1995
		JP	10279566 A	20-10-1998
		JP	2868313 B2	10-03-1999
		JP	4506222 T	29-10-1992
		KR	175310 B1	18-02-1999
		LT	586 A ,B	27-12-1994
		LU	90279 A9	21-10-1998
		LU	90371 A9	12-05-1999
		LV	10439 A ,B	20-02-1995
		MX	9203586 A1	01-07-1992
		NO	914528 A	17-01-1992
		NZ	237476 A	26-01-1994
		PL	293015 A1	08-02-1993
		PL	166581 B1	30-06-1995
		PL	166403 B1	31-05-1995
		PT	97078 A ,B	29-11-1991
		SG	49053 A1	18-05-1998
		SK	280096 B6	06-08-1999
		SK	283197 B6	04-03-2003
		RU	2099331 C1	20-12-1997
		US	5352788 A	04-10-1994
		US	5559233 A	24-09-1996
		ZA	9102072 A	25-03-1992
		AU	661017 B2	13-07-1995
		AU	2286892 A	11-03-1993
		CA	2077967 A1	11-03-1993
		CZ	9202759 A3	17-03-1993
		EP	0532410 A1	17-03-1993
WO 9938847 A	05-08-1999	AU	743018 B2	17-01-2002
		AU	2461599 A	16-08-1999
		CA	2318791 A1	05-08-1999
		EP	1060165 A1	20-12-2000
		HU	0100898 A2	28-02-2002
		JP	2002501946 T	22-01-2002
		WO	9938847 A1	05-08-1999

International Application No
PCT/US 03/22479

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9938847 A		US 6162922 A	19-12-2000